MAYO CLINIC
Cancer Center

Colon Cancer Family Registry

Volume 4, 2008

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Greetings

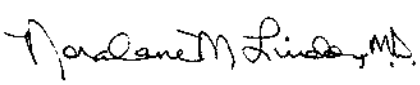
You make the difference!

Thank you for the honor of working with you and your family members. Together we can make significant progress toward the understanding of colorectal cancer.

It is the 10 year anniversary of the Colon Cancer Family Registry (previously called the Cooperative Family Registry for Colorectal Cancer Studies). Our partnership between scientists and families with colorectal cancer has led to significant advancements in our basic understanding of what causes colorectal cancer and what we can do to help prevent it. We continue to be vigorously engaged in a host of important projects that we all hope will lead to further advancements in our understanding of this cancer.

In this research news bulletin, we will provide a summary for you of the multitude of projects that have been made possible only because of involvement of families like yours. We want you to know how your efforts really are making a difference.

Thank you so very much for joining in partnership with us!



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Our Numbers are Growing

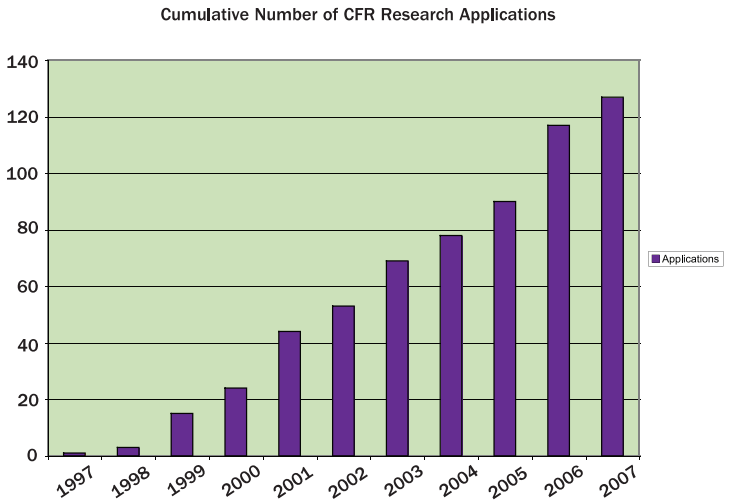
The Colon Cancer Family Registry (Colon CFR) remains the largest group of colon cancer families ever gathered together for research. This size allows us to conduct studies that were not possible before. We have the ability to discover the effects of environmental exposures and lifestyle differences that other studies were too small to understand. We can also search for genetic factors that may play major or minor roles in vulnerability to colorectal cancer. And ultimately, we can analyze how environmental factors interact with genetic factors. Mayo Clinic is one of six Colon CFR centers that began enrolling families in 1998. Today there are over 13,000 families enrolled from the United States, Canada, Australia, and New Zealand. This includes many families in which colorectal cancer has happened only one time as well as families in which many individuals have been diagnosed with colon cancer. The CFR enrolls men and women, older and younger people with colorectal cancer, families of all different ethnic backgrounds, as well as spouses and relatives who have not had cancer. Over 50,000 of those long risk-factor questionnaires have been completed by the families and controls that enrolled, just like you.

At the Mayo branch of the Colon CFR, we have enrolled more than 1,000 families and 4,000 individuals into our registry. We are so grateful to all those that have returned the blood samples and lifestyle questionnaires – we know how long that takes to complete! We also are so appreciative for the participation of over 496 spouses and 2,013 blood relatives who have not had any cancers. These individuals allow us the opportunity to compare similarities and differences between those with and without cancer.

If You Build It, They Will Come

As you may guess, the first few years of the Colon CFR were dedicated to enrolling families and entering a lot of information into secure databases. As sufficient numbers of families enrolled, the research became possible. We have tracked the number of projects begun each year and the trend is clear: there is a steady and impressive increase in research projects coming along based on the Colon CFR. For those of us who have worked to establish this registry, we are thrilled that scientists from all sorts of disciplines are utilizing their skills to research colorectal cancer. That was the original vision. It is becoming reality. Maybe this is a "Field of Dreams!"

As the number of research projects snowballs, it becomes increasingly challenging to tell you of all projects and their significance. However, we can report on some of our findings, and just the sheer number of projects is impressive. As you can see from this graph, requests for new projects have increased over time.



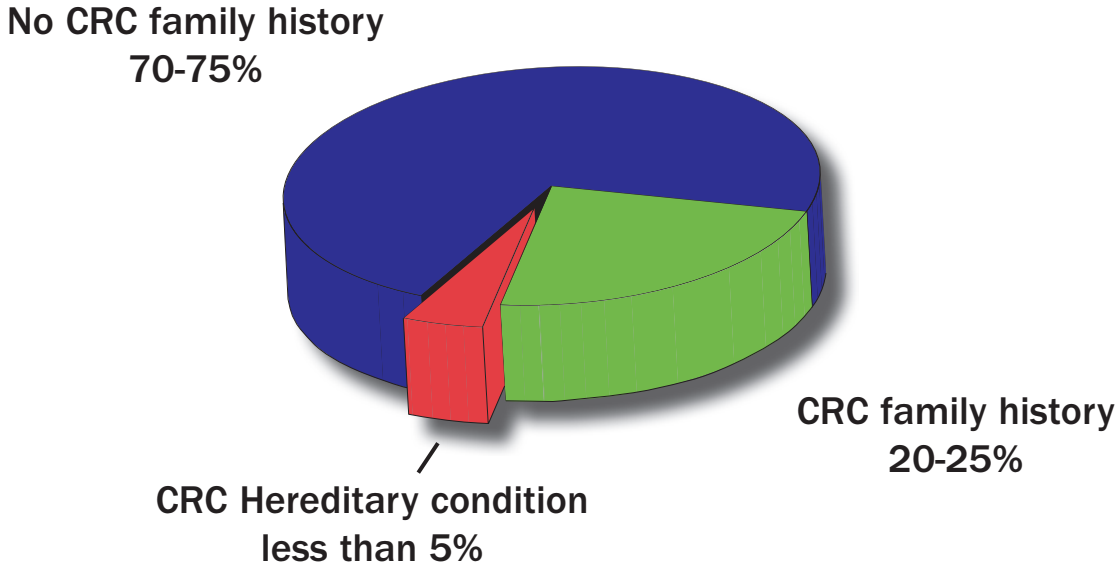
For Inquiring Minds: Genetics and Colorectal Cancer

Presently, it appears that about 5 percent of people who develop colon cancer have a hereditary condition; about 20 percent to 25 percent have a family history of colon cancer but no clear evidence for a fully hereditary condition, and about 70 percent to 75 percent have no history of colorectal cancer in the family. We refer to this latter group as "sporadic." The Colon CFR is studying all three groups.

Sporadic Colorectal Cancers – Overall, colorectal cancer (CRC) is diagnosed at an average of age 71 in the United States. Colorectal cancer is not rare: the lifetime risk for all Americans is about 5.5 percent or one in 18 people. Of those diagnosed, less than 1 percent are diagnosed under age 34, 3.6 percent between ages 35-44, 11 percent between ages 45-54, 18 percent between ages 55-64, 28 percent between age 65-74 and 41 percent over age 74 years.

Familial Colorectal Cancers – If you have a family history of someone with CRC, then your risk is more than the general population and you are encouraged to have regular colonoscopy to remove polyps. If you have a first degree relative (parents, brothers, sisters, adult children) diagnosed with CRC, your lifetime risk is about double. If your relative was young, or if you have multiple relatives with CRC, your risk is even higher.

Hereditary CRC – While only about 5 percent of all CRC is hereditary, it does affect people at younger ages, so impact on your life can be great. Hereditary disorders with increased risks for CRC include Lynch Syndrome, Familial Adenomatous Polyposis, MYH-associated polyposis, Juvenile Polyposis, Hyperplastic Polyposis, Li-Fraumeni Syndrome and Peutz-Jegher Syndrome. As we continue our research, we expect that some new disorders will be discovered. These are diagnosed by some combination of pedigree analysis, physical examination, colonoscopy, and genetic testing.



CFR Research in 2008

Calcium – It's not just about bones. Research has shown interaction between dietary calcium, vitamin D, and vitamin D gene receptor variation. A larger study on this promising topic is underway. This link appears to be one of the strongest associations that have emerged from studies of many, many environmental agents. It appears to be important to have adequate dietary calcium.

Hormones – It's not just about hot flashes. Dietary phytoestrogen (estrogen found in plants such as soy) was shown to be associated with a small reduction in risk for CRC in one study. Confirmatory studies are underway.

Smoking – It's not just about the lungs. The risk for the so-called MSI-high type of colorectal cancer appears to be increased in those who smoke. So our message for all patients is, of course, to not smoke, and to do whatever it takes to quit smoking. There are lots of good programs to help people quit smoking. Please talk with your doctor if you are interested in learning more, or visit: http://1800quitnow.cancer.gov/.

From data comes knowledge and from knowledge comes wisdom. The new genomics has brought with it major challenges, specifically how to interpret the massive amounts of data that can be generated in laboratories. Handling and analyzing this massive amount of data is a barrier to being able to bring benefit to patients. It is now much easier to run the lab test than to calculate what the result actually means – a new problem for scientists to have. The CFR registry has been involved with several recent publications using powerful computations systems to compare family-based studies with non family based, to understand the strengths and weaknesses of each approach and make the laboratory analyses more meaningful.

The mystery deepens. In the past year, several research groups discovered and confirmed that there is a variant in a region on chromosome 8 that is present in people who develop colorectal cancer more often than it is present in people who do not get colorectal cancer. Scientists focused intense attention to this area of the human genome, only to discover that there is no gene in this region. Apparently parts of the human genome that were formerly disregarded as "junk" DNA are, in fact, critical to the regulation of our genes. This recognition has opened up a whole new area of exploration. Nature is far more complex that anyone realizes, and we enjoy our continuing discoveries.

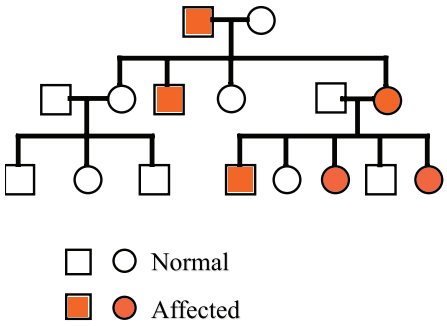
From the Participant's Viewpoint

"I feel privileged to be involved in this study, and I encourage others to participate. My mother had colon cancer and survived 35 years after diagnosis; my sister passed away at age 46 from colon cancer; two of my children have tested positive for a genetic condition that increases their risk for colon cancer. Hopefully this research will provide answers and help future generations make informed decisions. People who have incidences of colon cancer in their family should be aware of genetic disorders such as Lynch syndrome/ Hereditary Non-Polyposis Colon Cancer (HNPCC)."

Keith Warner
38 1/2 year colon cancer survivor (first incidence),
13 1/2 year colon cancer survivor (second incidence)

Hereditary Colon Cancers – The Colon CFR has been very active in studying those uncommon families that have identifiable genetic causes for the cancer in the families. Two conditions that are being evaluated intensively are the Lynch Syndrome (Hereditary Non Polyposis Colon Cancer Syndrome) and MYH-associated polyposis. Recently, genetic testing for these hereditary disorders was conducted for some, ***but not all***, families in the Colon CFR. After careful consideration by our Mayo research institutional review board, we were granted permission to offer these results back to the families on which testing had been done. Again, ***not all families were tested***. If this testing was conducted on your family, then all family members will receive a letter of explanation from us, explaining how participants can obtain their results if they want to know.

Genetic Linkage Studies - The current knowledge about hereditary and familial causes of colorectal cancer is extremely limited. It is possible that more genes are waiting to be discovered, and the Colon CFR is undertaking a project that will try to discover new genes that may cause colorectal cancer in some families. The project involves looking at families in which more than one person has developed colorectal cancer and comparing their genes with other family members who have never had cancer. By putting together this type of information on hundreds of such families, we hope to discover new genes that are important in the tendency to develop colorectal cancer.



Keeping the Mayo Colon CFR Up-To-Date:

How has your family history changed? When you originally enrolled in the Colon CFR, we collected a family history of cancers from all enrollees. Family histories change over the years with births, deaths, and new diagnoses. We therefore are updating all the family histories by a combination of phone calling and written questionnaires. This helps us have up-to-date information on what is happening in your family. It also provides an opportunity to invite more relatives into this study.

Inviting more family members to enroll. The Colon CFR is a **family** registry. We are interested in extending an invitation to enrollment to all first-degree relatives (parents, brothers, sisters, adult children) of people who have had colorectal cancer. Having lifestyle questionnaires and blood specimens from your relatives is enormously powerful to researchers who are trying to tease apart the differences between who gets cancer and who does not. It takes studying literally thousands of people to detect small differences that may protect or predispose them to colorectal cancer.

Frequently Asked Questions from CFR Participants:

Who has access to my CFR study information?
Access to your personal information is extremely limited and highly protected. Even if information you gave us is used in studies that involve other medical centers and even if your blood specimen is shared with researchers elsewhere, no one outside of our Mayo study group can know who you are. All information is given a code number and only the Mayo study group has the key to the code. Your privacy and confidentiality are safeguarded carefully. We understand how important this is to everyone. No results are entered into your Mayo medical record (if you have one here) and no insurance company has any access to anything we record or study. **Confidentiality is a top priority**. We try to handle all your information the way we would want ours handled if we were in this study.

***NOTE:** On May 21st of this year, President Bush signed into law the Genetic Information Nondiscrimination Act (GINA.) This legislation will be the first to prohibit employers and health insurers from discriminating against individuals on the basis of their genetic information. With the passage of this bill, people will be able to participate in research studies without the fear of genetic discrimination. Under the federal protection provided by GINA, health care practitioners will be able to recommend appropriate genetic testing and screening procedures unencumbered by the fear of discrimination based upon the results. The bill had passed the Senate unanimously and the House by a vote of 414 to 1. The long-awaited measure, which has been debated in Congress for 13 years, will pave the way for people to take full advantage of the promise of personalized medicine without fear of discrimination.*

Should I have genetic testing?
This question cannot be answered without knowing much more about you as a person. If your history suggests that the odds of having a genetic condition are very small (as is the case for most people with cancer), then it is probably not sensible to test. For those whose cancer history, family history, or tumor testing raise more concern for a hereditary cause for cancer, testing might be reasonable.

Genetic testing can have both risks and benefits. It is important to discuss the decision with a professional (such as a medical geneticist or genetic counselor) before undergoing genetic testing. Both positive and negative results can provide relief and reduce uncertainty about genetic status when a genetic test is used appropriately. A negative test may reduce the need for frequent checkups or surgeries and may create a sense of well being that one is not at increased risk for a disease compared to the general population. A positive test can increase knowledge and encourage an individual to use appropriate preventive measures to reduce risk.

From the Participant's Viewpoint

"I would like to thank the staff involved with the CFR study for the wonderful work that you are doing. You are gaining invaluable knowledge that will surely have a profound affect on the prevention of many forms of cancer for generations to come. I only hope that you will see the difference that you are making."

Beth Pierce

Does Mayo CFR provide free genetic counseling and genetic testing?
The Colon CFR is a research project and is not meant to provide individualized health care advice to you nor be a substitute for having a consultation with a geneticist or having testing done in a clinical laboratory if necessary. Some amount of genetic analysis is being done as part of specific projects, however, and if results are thought to be of high significance to you or your family, then under very restrictive rules, the Colon CFR staff may provide some genetic counseling via the phone in the context of telling you about your option of learning a research result. If you want to explore genetic testing, you should not rely on this study to give you what you need. We are happy to assist you in locating a geneticist in your area.

How long will the CFR study last?
An application for renewal for another four years has been submitted.

Will I find out the final results of the study?
We don't anticipate "final results" in this study, as it is an ongoing study. As we have discussed, there are over 100 individual projects underway that involve some proportion of all CFR enrollees. Any major finding will be published and we plan to continue newsletters such as this to keep you up-to-date. If something potentially highly useful to you is discovered about you individually, you will be contacted to see if you choose to learn about this or not. For many people, no individually useful results will ever be found.

How did you get my tumor block?
This question comes up quite frequently, particularly from participants who did not have surgery at Mayo Clinic. When a patient is first contacted and agrees to participate, they are sent a lot of information, a blood kit, consent form, epidemiology questionnaire and a medical authorization to obtain medical records and tissue blocks from their cancer surgery. When the patient (you) signs the medical authorization form, he or she also lists the name of the institution that we should contact to obtain those records and blocks. We then send this form, along with a letter requesting the material, to the facility listed on the form. Once the tissue blocks are received, slides are made (see next paragraph). The blocks are then returned to the institution.

What happens to my blood and tissue sample in this study?
After blood is drawn, it is sent immediately to Mayo Biospecimen Accessioning and Processing Laboratory. When the tubes arrive, their labels are checked to see that they agree with the paperwork that was sent with them – ensuring they are from the right person. A few drops of blood are spotted onto a special paper for studies that need only small amounts of blood. The remaining blood is spun in a centrifuge to separate the plasma (the liquid component of blood) from the cells. The plasma and the cells are then moved to smaller tubes and stored in a very cold freezer until it is needed for a research project.

For those who had a cancer removed, we may have requested written permission to release the stored tissue from the hospital where your surgery was performed. Once permission is provided, our staff requests the specimens (often called "tissue blocks" because they are embedded in rectangular pieces of wax) from that hospital.

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With the arrival of the blocks at Mayo Colon CFR area, blocks are logged into our database, and then ultra-thin slices of tumor tissue are carefully shaved off the blocks to make slides. The slides are examined by a pathologist and a report on that tumor is generated and also recorded in the database. The slides are stored at Mayo for research use but the original blocks are returned to your hospital.

How useful is colorectal cancer screening?
Colorectal cancer is highly preventable if polyps in the colon or rectum are removed. It is believed that nearly all colorectal cancers began as a polyp. It is estimated that only about 1 in 25 polyps will turn into a cancer, but no one can tell which polyp might become a cancer. Therefore, colonoscopic screening with removal of polyps actually prevents colorectal cancers.

How often should colon cancer screening be done?
In March 2008, the American Cancer Society (ACS), the American College of Radiology and the U.S. Multi-Society Task Force on Colorectal Cancer (a group that comprises representatives from the American College of Gastroenterology, American Gastroenterological Association, and American Society for Gastrointestinal Endoscopy), released consensus guidelines for colorectal cancer screening. While these may not be applicable to many of the Colon CFR families, in general, adults age 50 and older are recommended to have regular screening for colorectal cancer using one of the following methods:

Colorectal Cancer Screening Guidelines for Average Risk Persons

- Yearly guaiac-based fecal occult blood test or fecal immunochemical test — tests that check for blood in the stool and have a high sensitivity for cancer
- Flexible sigmoidoscopy every five years
- Colonoscopy every 10 years
- Double contrast barium enema every five years
- Stool DNA test – shown effective, although at this time the recommended interval is unknown
- CT colonography every five years

But if you are in this study, you might not be considered "average risk." The American Cancer Society provides separate guidelines for screening those at increased and high risk. These are shown in the following table. (see next page)

American Cancer Society Guidelines on Screening and Surveillance for the Early Detection of Colorectal Adenomas and Cancer in People at Increased Risk or at High Risk

Risk Category	Age to Begin	Recommended Test(s)	Comment
INCREASED RISK – Patients With a History of Polyps on Prior Colonoscopy			
People with small rectal hyperplastic polyps	Same as those with average risk	Colonoscopy, or other screening options at regular intervals as for those at average risk	Those with hyperplastic polyposis syndrome are at increased risk for adenomatous polyps and cancer and should have more intensive follow-up.
People with 1 or 2 small (less than 1 cm) tubular adenomas with low-grade dysplasia	5 to 10 years after the polyps are removed	Colonoscopy	Time between tests should be based on other factors such as prior colonoscopy findings, family history, and patient and doctor preferences.
People with 3 to 10 adenomas, or a large (1 cm +) adenoma, or any adenomas with high-grade dysplasia or villous features	3 years after the polyps are removed	Colonoscopy	Adenomas must have been completely removed. If colonoscopy is normal or shows only 1 or 2 small tubular adenomas with low-grade dysplasia, future colonoscopies can be done every 5 years.
People with more than 10 adenomas on a single exam	Within 3 years after the polyps are removed	Colonoscopy	Doctor should consider possibility of genetic syndrome (such as FAP or HNPCC).
People with sessile adenomas that are removed in pieces	2 to 6 months after adenoma removal	Colonoscopy	If entire adenoma has been removed, further testing should be based on doctor's judgment
INCREASED RISK – Patients With Colorectal Cancer			
People diagnosed with colon or rectal cancer	At time of colorectal surgery, or can be 3 to 6 months later if person doesn't have cancer spread that can't be removed	Colonoscopy to view entire colon and remove all polyps	If the tumor presses on the colon/rectum and prevents colonoscopy, CT colonoscopy (with IV contrast) or DCBE may be done to look at the rest of the colon.
People who have had colon or rectal cancer removed by surgery	Within 1 year after cancer resection (or 1 year after colonoscopy to make sure the rest of the colon/rectum was clear)	Colonoscopy	If normal, repeat exam in 3 years. If normal then, repeat exam every 5 years. Time between tests may be shorter if polyps are found or there is reason to suspect HNPCC. After low anterior resection for rectal cancer, exams of the rectum may be done every 3 to 6 months for the first 2 to 3 years to look for signs of recurrence.
INCREASED RISK – Patients With a Family History			
Colorectal cancer or adenomatous polyps in any first-degree relative before age 60, or in 2 or more first-degree relatives at any age (if not a hereditary syndrome).	Age 40, or 10 years before the youngest case in the immediate family, whichever is earlier	Colonoscopy	Every 5 years.
Colorectal cancer or adenomatous polyps in any first-degree relative aged 60 or higher, or in at least 2 second-degree relatives at any age	Age 40	Same options as for those at average risk.	Same intervals as for those at average risk.
HIGH RISK			
Familial adenomatous polyposis (FAP) diagnosed by genetic testing, or suspected FAP without genetic testing	Age 10 to 12	Yearly flexible sigmoidoscopy to look for signs of FAP; counseling to consider genetic testing if it hasn't been done	If genetic test is positive, removal of colon (colectomy) should be considered.
Hereditary non-polyposis colon cancer (HNPCC), or at increased risk of HNPCC based on family history without genetic testing	Age 20 to 25 years, or 10 years before the youngest case in the immediate family	Colonoscopy every 1 to 2 years; counseling to consider genetic testing if it hasn't been done	Genetic testing should be offered to first-degree relatives of people found to have HNPCC mutations by genetic tests. It should also be offered if 1 of the first 3 of the modified Bethesda criteria is met.1
Inflammatory bowel disease -Chronic ulcerative colitis -Crohn's disease	Cancer risk begins to be significant 8 years after the onset of pancolitis (involvement of entire large intestine), or 12-15 years after the onset of left-sided colitis	Colonoscopy every 1 to 2 years with biopsies for dysplasia	These people are best referred to a center with experience in the surveillance and management of inflammatory bowel disease.

[1]*The Bethesda criteria can be found in the "Can Colorectal Cancer Be Prevented?" section of our larger Colorectal Cancer document.*

Genetic Testing: A Review

Because genetic testing results are being offered to some Colon CFR participants, we are including general information about this subject.

What is genetic testing?

- A genetic test can be used to confirm a disease diagnosis or to look for a future predisposition to a disease.
- A genetic test is usually done by a simple blood test but can also be done by testing other body fluids or tissues.
- Genes are made up of DNA, the information in our cells that instructs the body how to grow and function.
- DNA is coded by four chemicals, which are symbolized by the letters A, C, G and T (adenine, cytosine, guanine, and thymine).
- A genetic test looks for changes, or mutations, in the DNA, which could lead to a disease. Such changes can be as small as a single altered chemical (such as "A" changed to a "C"). Other changes could be much larger, such as a loss of several hundred or thousand chemicals.

Note: The cause of colorectal cancer is still unknown for most people. Less than 5 percent of colorectal cancer is thought to be hereditary. The majority of people who get cancer do not inherit altered genes as the cause of their colorectal cancer, and most Colon CFR participants do not have a recognizable genetic disorder.

Colon Cancer Family Registry Staff

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QUESTIONS?

Please call the number below at any time if you have questions regarding the Colon CFR study or to report any changes in the family history you provided earlier. We always welcome feedback. Please let us know if you have moved or anticipate a change in address. *Please note our new Colon CFR email address.*

1-866-514-8452 (toll free)

New Colon CFR Email address

colonCFR@mayo.edu

New Colon CFR Web site

The National Cancer Institute now has a public web site featuring the Colon CFR. The web site is: **http://epi.grants.cancer.gov/CFR/**

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